REMARKS

Amendments

Claim 15 is amended to recite that the osmolality is from 250 to 350 mOsmol/kg, thereby avoiding duplication with claim 10. Claim 18 is amended to correct an obvious grammatical error.

Response to Notice to Comply with the Sequence Requirements 37 CFR §§1.821-825

In the Office Action and the attached Notice to Comply, it is asserted that the application contains nucleotide and/or amino acid sequences that require compliance with 37 CFR §§1.821-825. Applicants disagree.

Applicants contend that the instant application does not contain sequence data pursuant to 37 CFR §1.821(a)(2). The sequences presented at pages 2 and 6 of the specification and recited in claim 18 contain D-amino acids. Thus, a Sequence listing is not required (*i.e.*, "[t]hose sequences containing D-amino acids are not intended to be embraced by this definition"). Therefore, applicants respectfully request withdrawal of said Notice. Favorable reconsideration of the application is respectfully requested.

Rejection under 35 USC §103

Claims 1-23 are rejected as allegedly being obvious in view of Jonczyk et al. (US 6,001,961) in view of Muller et al. (WO 85/02767) and Vasudevan et al. (WO 00/62793). This rejection is respectfully traversed.

The rejection alleges that it would be obvious to the combine the oligopeptides of Jonczyk et al. with the etherified cyclodextrins of Muller et al. However, the teaching of Muller et al. suggests away from such a combination.

The Muller et al. disclosure is directed to increasing the solubility and water stability of poorly soluble drugs. This asserted improvement in solubility/stability is obtained by forming an inclusion compound between the poorly soluble drug and β-cyclodextrins. As described at page 3, lines 15-20, the β-cyclodextrins and the poorly soluble, water-instable drug form an inclusion compound which leads to enhanced solubility and water stability of

the drug. See also the discussion of Muller et al. in applicants' specification at page 4, lines 5-15.

In Example 2, Muller et al. describe increasing the solubility of the drugs indomethacine, digitoxine, progesterone, dexamethasone, hydrocortisone, and diazepam as by the formation of cyclodextrin inclusion compounds. See Table 2. These compounds all have poor solubility with saturation solubilities within the range of 0.002-0.36 mg/ml. As shown in Example 3 and Table 3, indomethacine is an example of a water instable compound whose stability is increased by the formation of the cyclodextrin inclusion compound.

In comparison, the drug compounds of applicants' composition are peptides and thus have relatively good solubility in water. For example, cilengitide has a comparatively high saturation solubility of 19 mg/ml in physiologic NaCl solution. Additionally, the peptides of the invention are relatively stable. Moreover, efforts directed to increasing the solubility of the peptides by adjusting pH actually resulted in decreasing stability. See page 3, line 14-page 4, line 3 of applicants' specification. Hence, since the objective of Muller et al. is to increase the solubility and enhance the stability of poorly soluble drug compounds, one of ordinary skill in the art would not be motivate to use its disclosure to modify compounds, like applicants' peptides, that have relatively good solubility and water stability.

Moreover, to form the inclusion compounds described by Muller et al., the drug in question must be able to fit within the hydrophobic cavity formed by the rings of the cyclodextrin. See the disclosure by Muller et al. at page 5, lines 27-30. Thus, the drug must be of a low molecular weight and a small spatial size. This is further evidenced by the drugs described in Muller et al., all of which are of low molecular weight and small spatial size. See the list of drugs at page 6 of Muller et al.

Conversely, applicants' peptides have a relatively high molecular weight and further are cyclic and spatially large in comparison. See also applicants' specification at page 4, lies 12-15. Thus, since formation of the inclusion compounds of Muller et al. require the drug agents to be of low molecular weight and small size, one of ordinary skill in the art would not look to such a disclosure for purposes of modifying the solubility of compounds like applicants' cyclic peptides.

The rejection alleges that, in light of the disclosure of Vasudevan et al., one of ordinary skill in the art would have a reasonable expectation of success for improving the

solubility and stability of the cyclic peptides Jonczyk et al. by combining them with cyclodextrins. Applicants' disagree. The Vasudevan et al. disclosure is not directed to cyclic peptides in general, but instead is directed to a particular type of cyclic peptide having a structural that is believed to interact with the cyclodextrin.

The disclosure of Vasudevan et al. concerns reducing the adverse effects associate with injecting pseudomycins, or related lipodepsidecapeptides, in the treatment of fungal infections, by combing the pseudomycin or lipodepsidecapeptide with a hydroxypropyl-β-cyclodextrin or sulfobutylether-β-cyclodextrin. See page 2, lines 16-30 and the text bridging pages 14-15.

As shown at pages 3-4, pseudomycins and the related lipodepsidecapeptides are cyclic peptides having a lipophilic moiety extending from the cyclic structure. See also page 5, lines 18-23 wherein it is stated:

> A pseudomycin is a lipodepsidecapeptide, a cyclic peptide including one or more unusual amino acids and having one or more appended hydrophobic or fatty acid side chains. Specifically, the pseudomycins are lipodepsinanopeptides, with a cyclic peptide portion closed by a lactone bond and including the unusual amino acids 4-chlorothreonine (CLThr), 3-hydroxyaspartic acid (HOAsp), 2,3-dehydro-2-aminobutyric acid (Dhb), and 2,4-diaminobutyric acid (Dab).

At page 16, lines 3-16, Vasudevan et al. discuss their theory as to the cause of the adverse effects associated with administering pseudomycins and how such effects are ameliorated by the cyclodextrin composition. Due to the hydrophobic long fatty acid chain extending from the cyclic peptide of pseudomycins, it is believed that these agents might form micelles in aqueous solutions or blood. To reduce damage caused by such soluble aggregates, one possibility would be to add an agent that that forms a complex with the fatty acid chain, i.e., a complex with a cyclodextrin or substituted cyclodextrin.

Clearly, one of ordinary skill in the art would recognize that the disclosure of Vasudevan et al. is directed to a particular problem, reducing the adverse effects associate with administering pseudomycins. Furthermore, Vasudevan et al. describe a possible mechanism by which such adverse effects are reduced, a mechanism which involves the

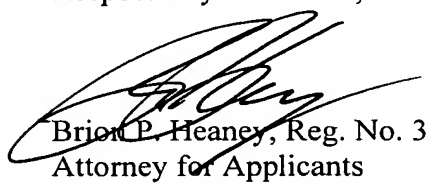
formation of a complex between the particular long fatty acid chain present in pseudomycins. Thus, one of ordinary skill in the art would not look to the disclosure of Vasudevan et al. to increase the solubility of structurally different cyclic peptides, such as the cyclic peptides of applicants' claimed compositions.

Thus, it is respectfully submitted that the rejection fails to present sufficient motivation that would lead one of ordinary skill in the art to modify the peptides compositions of Jonczyk et al. in such a manner as to arrive at a composition in accordance with applicants' claimed compositions. Contrary to the assertions in the rejection, the disclosure of Muller et al. does not suggest combing cyclic peptides with cyclodextrins, and the disclosure of Vasudevan et al. does not suggest combing the cyclic peptides of Jonczyk et al. with cyclodextrins.

In view of the above remarks, it is respectfully submitted that Jonczyk et al., taken alone or in combination with Muller et al. and/or Vasudevan et al., fails to render obvious applicants' claimed invention. Withdrawal of the rejection is respectfully requested.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,



Brion P. Heaney, Reg. No. 32,542
Attorney for Applicants

MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
Arlington Courthouse Plaza 1
2200 Clarendon Boulevard, Suite 1400
Arlington, VA 22201
Direct Dial: 703-812-5311
Facsimile: 703-243-6410
Attorney Docket No.: MERCK-2955

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